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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/756,830	01/08/2001	Sydney Brenner	5525-0046.30	6856

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PERKINS COIE LLP
P.O. BOX 2168
MENLO PARK, CA 94026

EXAMINER	
SISSON, BRADLEY L	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/756,830	BRENNER ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,15 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Location of Application

1. The location of the subject application has changed. The subject application is now located in Workgroup 1630, Art Unit 1634, and has been docketed to Primary Examiner Bradley L. Sisson.

Specification

2. The specification is objected to as documents have been improperly incorporated by reference. In particular, the specification states at page 4, last paragraph, that PCT documents and an allowed application "are incorporated by reference." Such omnibus language fails to specify what specific information applicant seeks to incorporate by reference and similarly fails to teach with detailed particularity just where that specific information is to be found in each of the cited documents. As set forth in *Advanced Display Systems Inc. v. Kent State University* (Fed. Cir. 2000) 54 USPQ2d at 1679:

> Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes it clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USQP 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). **To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents.** *See In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-02, 170 USPQ 213, 216-17 (CPA 1971) (reasoning that a rejection or anticipation is appropriate only if one reference "expressly

> incorporates a particular part" of another reference); *National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230, 123 USPQ 279, 283 (6th Cir. 1959) (requiring a specific reference to material in an earlier application in order to have that material considered a part of a later application); *cf. Lund*, 376 F.2d at 989, 13 USPQ at 631 (holding that **a one sentence reference to an abandoned application is not sufficient to incorporate from the abandoned application into a new application**). (Emphasis added.)

Accordingly, the cited documents are not considered to have been properly incorporated by reference and as such, have not been considered with any effect towards their fulfilling, either in part or in whole, the enablement, written description, or best mode requirements of 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-7 and 15-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Attention is directed to the decision in *University of Rochester v. G.D. Searle & Co.* 68 USPQ2D 1424 (Fed. Cir. 2004) at 1428:

> To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Vas-Cath, 935 F.3d at 1563; see also Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"); In re Gosteli, 872 F.2d 1008, 1012

[10 USPQ2d 1614] (Fed. Cir. 1989) ("the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed"). Thus, an applicant complies with the written-description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572.

5. For convenience, claims 1 and 15 are reproduced below.

1. (Original) A method of synthesizing a repertoire of oligonucleotide tags of a predetermined length, the method comprising the steps of:

(a) providing a repertoire of oligonucleotide tag precursors in an amplicon, the oligonucleotide tag precursors each comprising one or more words, and each of the one or more words being selected from the same minimally cross-hybridizing set;

(b) cleaving the amplicon at a word in each of the oligonucleotide tag precursors to form one or more ligatable ends on each oligonucleotide tag precursor;

(c) ligating one or more words to the one or more ligatable ends to elongate each of the oligonucleotide tag precursors;

(d) amplifying the elongated oligonucleotide tag precursors in the amplicon; and

(e) repeating steps (b) through (d) until a repertoire of oligonucleotide tags having the predetermined length is formed.

15. (Currently amended) A repertoire of cloning vectors for attaching oligonucleotide tags to polynucleotides, wherein each of the vectors comprises a double stranded element corresponding to an oligonucleotide tag of the form:

$$w_1(N)_{x1}w_2(N)_{x2} \ldots (N)_{xn-1}w_n$$

wherein

each of w_1 through w_n is a word consisting of an oligonucleotide having a length from three to fourteen nucleotides or basepairs and being selected from the same minimally cross hybridizing set, wherein a word of the set and a complement of any other word of the set has at

least two mismatches;

N is a nucleotide;

each of x_1 through x_{n-1} is an integer selected from the group consisting of 0, 1, and 2, ~~3, and 4~~; provided that at least one of x_1 through x_{n-1} is 1 or [[,]] 2~~, 3, or 4~~; and

n is an integer in the range of from 4 to 10.

6. For purposes of examination, the "repertoire of oligonucleotide tags" to be synthesized by the method of claim 1 can be of virtually any length and nucleotide composition. Acknowledgement is made of the specification providing a definition of "word" at page 4, which for convenience, is reproduced below.

> As used herein, the term "word" means an oligonucleotide selected from a minimally cross-hybridizing set of oligonucleotides, as disclosed in U.S. patent 5,604,097; International patent application PCT/US96/09513; and allowed U.S. patent application Ser. No. 08/659,453; which references are incorporated by reference. An oligonucleotide tag of the invention consists of

7. The aspect of being able to accurately and reproducibly identify "minimally cross-hybridizing set[s] of oligonucleotides" is critical to the claimed method. As noted above, the cited documents have been improperly incorporated by reference and a such, cannot not be relied upon for satisfaction of written description requirements under 35 USC 112, first paragraph.

Page 9, first full paragraph, further identifies preferred embodiments and directs the skilled artisan to various publications. Said publications, and preferred embodiments, including preferred algorithms, have not been incorporated by reference. Accordingly, the specification has not provided an adequate written description of the preferred embodiments of the claimed method. While applicant may assert that certain embodiments of the claimed invention may be obvious to those of skill in he art, obviousness cannot be relied upon for satisfaction of the written description requirement of 35 USC 112, first paragraph. It appears that applicant is attempting to satisfy the written description requirement of 35 USC 112, first paragraph, through obviousness. In support of this position, attention is directed to the decision in *University of California v. Eli Lilly and Co.* (Fed. Cir. 1997) 43 USPQ2d at 1405, citing *Lockwood v. American Airlines Inc.* (Fed. Cir. 1997) 41 USPQ2d at 1966:

> Recently, we held that a description which renders obvious a claimed invention is not sufficient to satisfy the written description requirement of that invention.

8. While claim 1 is directed to a method of producing a repertoire of oligonucleotide tags, claims 15 and 16 are directed to "a repertoire of cloning vectors." A review of the disclosure fails to find an adequate written description of such a repertoire. At best the disclosure provides suggestions as to how such a repertoire could be produced, but as shown above, such disclosure does not adequately describe how they are to be produced, even when the method is considered in terms of the preferred embodiments.

9. It is well settled that one cannot claim that which they do not yet posses. A review of the disclosure fails to find an adequate written description of the entire genus of vectors so as to reasonably suggest that applicant, at the time of filing, was in possession of same.

10. For the above reasons, and in the absence of convincing evidence to the contrary, claims 1-7 and 15-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Claims 1-7 and 15-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

11. As set forth above, claims 1-7 are drawn to a method of making oligonucleotide tags, wherein said method fairly encompasses the use of vectors that are also produced by the method. Disclosures critical to enabling the claimed method are not properly incorporated by reference. Indeed, even the preferred embodiments are not found within the four corners of the instant application.

12. The claimed method fairly encompasses producing a repertoire of oligonucleotides that can be of virtually any length. The specification, however, cautions artisans not to produce oligonucleotides above 40-50 nucleotides in length. A review of the specification fails to produce an enabling disclosure whereby skilled artisan are able to overcome the admitted difficulty associated with producing oligonucleotides of such lengths.

13. Assuming *arguendo*, that the claimed oligonucleotides and vectors could be produced, the specification does not enable the use of said oligonucleotides and vectors.

14. The specification provides the following examples:

a. Example 1, "Repertoire Synthesis by Repeated Cycles of Cleavage, Self-Selection, Ligation, and Amplification," pages 14-16;

b. Example 2, "Repertoire Synthesis by Convergent Assembly of Error-free Oligonucleotide Tag Precursors," pages 16-18;

c. Example 3, "Construction of an Eight-Word Tag Library," pages 18-24.

Clearly, the three examples do not each the skilled artisan how to recognize useful over non-useful oligonucleotides or vectors.

15. In view of the breadth of scope clamed, the limited guidance provided, the unpredictable nature of the art to which the claimed invention is directed, and in the absence of convincing evidence to the contrary, the claims are not enabled by the disclosure.

16. Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

17. Claim 1 recites the limitation "the same minimally cross-hybridizing set" in step (a). There is insufficient antecedent basis for this limitation in the claim. Claims 2-7, which depend from claim 1, fail to overcome this issue and are similarly rejected.

18. Claim 7 is indefinite with respect to what the units are referencing. Specifically, claim 7 refers to the word having "a length of four." Similar issues of indefiniteness exist with respect to a length of "18-40."

Claim Rejections - 35 USC § 102

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20. Claims 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Stratagene Cloning Systems (1993, page 27).

21. In accordance with claim 15, the repertoire of cloning vectors can be of virtually any sequence, having a minimum size of 12 nucleotides

22. The Stratagene Catalog teaches a repertoire of cloning vectors (i.e. the pBluescript® II phagmids), which meets all of the limitations recited in Claims 15-16. Admittedly, the Stratagene Catalog does not teach the oligos that make up the "words (i.e. the 'w' in the formula recited) are "selected from the same minimally cross-hybridizing set wherein a word of the set and a complement of any other word of the set has at least two mismatches; N is a nucleotide; each of x_1 through x_{n-1} is an integer selected from the group consisting of 0, 1, 2, 3, and 4, provided that at least one of x1 through xn-l is 1, 2, 3, or 4; and n is an integer in the range of from 4 to 10,".

23. However, these limitations relate to how the repertoire of cloning vectors is to be made. It is well established that a product is not limited by how it is made but rather by its structure. If the product in a claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process, In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985).

24. In addition, the examiner admits that the Stratagene Catalog does not teach that their repertoire of cloning vectors (*i.e.*, the pBluescript® 11 phagmids) is to be used for "attaching oligo tags to polynucleotides". However, it is also well established that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art In order to patentably distinguish the claimed invention from the prior art. If the prior ad structure is capable of performing the intended use, then it meets the claim. *In re Casey*, 152 USPQ 235 (CCPA 1967)', *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Response to argument

25. At page 5 of the response received 06 April 2004, hereinafter the response, applicant asserts that the prior art does not each the limitation of $(N)_{xn}$, where xn has a value of 1 or 2.

26. This argument is not persuasive, as applicant is arguing limitations not present in the claims. It is noted with particularity that the value of x1 through xn-1 can be zero (0). Using such a value (0), there is no nucleotide N between the words.

27. For the above reasons, and in the absence of convincing evidence to the contrary, the rejection is maintained.

Conclusion

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

29. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

30. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

B. L. Sisson

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS
27 June 2004